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10/776,333	02/10/2004	Michael Moshman	077350.0136	1725

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EXAMINER	
MERCIER, MELISSA S	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
06/23/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/776,333	MOSHMAN ET AL.	
	Examiner	Art Unit	
	MELISSA S. MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-23* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-17 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt of Applicants Remarks and Amended Claims filed on March 19, 2008 is acknowledged. Claims 1-2 and 4-23 are pending in this application. Claims 18-19 remain withdrawn from consideration. Therefore, claims 1-2, 4-17, and 20-23 are under prosecution in this application. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Specification

The disclosure is objected to because of the following informalities: Applicant has submitted amendments to the specification, which are new matter. Applicant has presented amendments, which would change the release profile from first order to zero order kinetics.

Appropriate correction is required.

Response to Arguments

Applicant argues the release profile is as originally set forth in the figures and examples of the application as-filed: a substantially linear absorption rate. *See, e.g.,* page 16, lines 11-12 of the application as filed, noting the linear curves for formulations containing chitosan. Applicants are merely attempting to correctly reference such linear absorption as zero-order kinetics. Applicant has not demonstrated zero order kinetics in

the figures of the application. Zero order kinetics is defined as reactions independent of concentration of the reactants. A reaction of zero order is demonstrated if concentration data are plotted versus time and the result is a straight line. The only figure with a straight line presents is figure 6, however, the axis are AUC and dosage amounts. Furthermore, the plots are not to scale and if drawn to scale, would not result in a linear plot.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation of claim 6 is to use purified morphine, however, since the since the prior art disclose morphine to be used in pharmaceutical compositions, it is the examiners position that one of ordinary skill would use purified morphine.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues claim 6 further limits claim 1, since claim 1 does not require the use of purified morphine base monohydrate. Applicant also states in the response to the 112, 2nd paragraph rejection of claim 6, that pharmaceutical grade morphine base monohydrate is generally purified. Therefore, it is submitted that the morphine in claim 1 is inherently purified and since Applicant has not provided a desired purity level, any

morphine suitable for use in a pharmaceutical formulation would read on the instantly claimed morphine.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-2, 4-17, 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what a "therapeutically effective" and "an effective amount" are. It is unclear exactly how much is effective and what the desired effect actually is.

It is unclear what absorption rate is characterized by being "substantially linear". Applicant has not defined the parameters of substantially, nor provided any means for the examiner to ascertain the meaning.

Regarding claim 6, it is unclear what applicant is claiming by purified morphine. A specific purity is not defined by the claim and the examiner has no means of ascertaining the intended limitation. The examiner has interpreted purified to mean pharmaceutical grade.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues one of ordinary skill would be able to ascertain the effective amounts, however, the claims do not recited what the amount if effective for, i.e. pain

management, or controlled increase in plasma levels during the absorption phase therefore, the claim language is deemed indefinite. It is not clear based on the claim language what the component is effective for.

Applicant's arguments regarding the morphine base monohydrate as discussed above in the objection to claim 6.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-2, 4-8, 16-17, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US Patent 5,629,011) in view of Merck Index Monograph 06276

Illum discloses a composition for nasal administration of polar metabolites of opioid analgesics, including metabolites of morphine; and an absorption-promoting agent, including chitosan (abstract). Chitosan is discloses a being employed to improve the dissolution of poor soluble drugs or for sustained release of drugs by a process of slow erosion from a hydrated compressed matrix (column 3, lines 39-48). Illum discloses the concentration of the cationic polymer is present in the amount of 0.01-50% w/v (column 4, lines 5-7). Illum discloses the preparation of chitosan micro spheres comprising chitosan dissolved in water with a morphine metabolite incorporated into the micro sphere in which the particles may have variable controlled release characteristics through modifications made to the micro sphere system, for example by controlling the

degree of cross-linking or by the incorporation of excipient that alter the diffusion properties of he administered drug (column 6, lines 30-65).

Illum does not disclose the morphine is morphine base monohydrate.

The Merck index discloses generic morphine is in monohydrate form.

The instant claims differ from the references only in the specific percentage selected for the compositions. However, It would have been deemed prima Facie obvious to one having ordinary skill in the art at the time of the invention to optimize the percentage of active ingredient and the controlled releasing polymer, to prepare a composition containing a therapeutically effective amount of an active agent because the determination of a specific percentage having the optimum therapeutic effect is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the active compounds. Therefore, the invention as Whole has been prima face obvious to one of ordinary skill in the art at the time the invention was made.

Applicant is reminded that where the general conditions of the claims are met, burden is shitted to applicant to provide a patentable distinction. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. See In re Aller, 220 F.2d 454 105 USPQ 233,235 (CCPA 1955).

Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various transmucosal compositions having various amounts of the active agent and chitosan

polymers is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. See In re Russell, 439 F.2d 1228 169 USPQ 426(CCPA 1971).

Claims 1-2, 4-17 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum et al. (US Patent 6,387,917) in view of Merck Index Monograph 06276

Illum discloses a methane sulphonate salt of morphine and compositions thereof having medicinal uses, particularly for the treatment of pain and adapted for nasal delivery (abstract). The preferred composition comprises aqueous solutions in which the methane sulphonate salt is combined with chitosan to provide an increased absorption of the drug (column 2, lines 61-68). The morphine methane sulphonate liquid formulation will comprise 0.1mg/mL to about 600mg/mL (column 4, lines 20-24). The formulation may also be incorporate into formulations suitable for oral, buccal, rectal, or vaginal administration (column 4, lines 39-42). Illum's Examples 2-3 discloses a solution for intranasal administration comprising morphine base (monohydrate) and chitosan (column 5, line 33 through column 6, line 21).

Illum further discloses the formulation can also contain other ingredients such as buffer systems, pH modifiers, anti-oxidants, stabilizing agents, anti-microbial agents, chelating agents, viscosity-enhancing agents, or other agents generally used in

pharmaceutical formulations (column 4, lines 25-29). Applicants have defined the antioxidants as being used to adjust the pH of the composition (Specification, page 8, lines 3-11); therefore, it is the examiners position that it would have been obvious to a person of ordinary skill in the art to use methanesulphonic acid, citric acid, sodium citrate, or sodium ascorbate to adjust the pH of the composition.

Illum does not disclose the morphine is morphine base monohydrate.

The Merck index discloses generic morphine is in monohydrate form.

It is generally considered to be prime facie obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose in order to form a composition that is to be used for an identical purpose. The motivation for combining them flows from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose. As shown by the recited teachings, instant claims are no more than the combination of conventional components of pH adjusting components and antimicrobial agents. It therefore follows that the instant claims define prime facie obvious subject matter. Cf. In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

The instant claims differ from the references only in the specific percentage selected for the compositions. However, It would have been deemed prima Facie obvious to one having ordinary skill in the art at the time of the invention to optimize the percentage of active ingredient and the controlled releasing polymer, to prepare a composition containing a therapeutically effective amount of an active agent because the determination of a specific percentage having the optimum therapeutic effect is well

within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the active compounds. Therefore, the invention as Whole has been prima face obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various transmucosal compositions having various amounts of the active agent and chitosan polymers is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. See In re Russell, 439 F.2d 1228 169 USPQ 426(CCPA 1971).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues the morphine base monohydrate in Example 2 of Illum is converted to the methane sulphonate salt of morphine upon the addition of 2M methane sulphonic acid. This occurs prior to the addition of the chitosan solution. The examiner notes that applicant has employed the terminology comprising allowing for the inclusion/addition of any number of components regardless of their material effect on the other components.

While the reference teaches the equimolar amounts of acid to the morphine base, a conjugate base would be present and equilibrium would be established. Therefore, barring a showing to the contrary, it is it the examiners position that some morphine base monohydrate would still be present in the final product.

Applicant is reminded of MPEP 2123, which states the use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

Claims 1-2, 4-12, 16-17, 20-21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (US Patent 5,955,502) in view of Merck Index Monograph 06276.

Hansen discloses the use of a fatty acid ester as bioadhesive substances and methods for administering an active or protective substance to undamaged or damaged skin or mucosa of an animal such as a human by combining the active substance with a bioadhesive fatty acid ester. The mucosa can include oral, aural, nasal, lung, gastrointestinal, vaginal and rectal mucosa (abstract).

The composition of Hansen further comprises chitosan (column 12, lines 59-64), active agents, including morphine (column 11, line 25), antioxidants, including ascorbic acid and derivatives (column 14, lines 64-68), and antimicrobials (column 10, lines 23-24).

Applicants have defined the antioxidants as being used to adjust the pH of the composition (Specification, page 8, lines 3-11), therefore, it is the examiners position that it would have been obvious to a person of ordinary skill in the art to use methanesulphonic acid, citric acid, sodium citrate, or sodium ascorbate to adjust the pH of the composition.

Hansen does not disclose the morphine is morphine base monohydrate.

The Merck index discloses generic morphine is in monohydrate form.

It is generally considered to be prime facie obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose in order to form a composition that is to be used for an identical purpose. The motivation for combining them flows from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose. As shown by the recited teachings, instant claims are no more than the combination of conventional components of pH adjusting components and antimicrobial agents. It therefore follows that the instant claims define prime facie obvious subject matter. Cf. In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

The instant claims differ from the references only in the specific percentage selected for the compositions. However, It would have been deemed prima Facie obvious to one having ordinary skill in the art at the time of the invention to optimize the percentage of active ingredient and the controlled releasing polymer, to prepare a composition containing a therapeutically effective amount of an active agent because the determination of a specific percentage having the optimum therapeutic effect is well

within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the active compounds. Therefore, the invention as Whole has been prima face obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various transmucosal compositions having various amounts of the active agent and chitosan polymers is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. See In re Russell, 439 F.2d 1228 169 USPQ 426(CCPA 1971).

Claims 1-2, 4-17, and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dellamary et al. (US Patent 6,433,040) in view of Merck Index Monograph 06276.

Dellamary discloses methods, systems, and compositions comprising relatively stable dispersions of perforated microstructures in a suspension medium that are preferably administered vial liquid doe instillation, both for topical delivery to the lung and for delivery via the lung to the systemic circulation (column 1, lines 16-25). The composition may also be administered topically, subcutaneously, intramuscularly, intraperitoneally, nasally, vaginally, rectally, orally, or ocularly (column 9, lines 62-65). The dispersion comprising a structural matrix defining the perforated microstructure and

may comprising polysaccharides such as chitosan (column 18, lines 2-7). Dellamary discloses those skilled in the art will appreciate that by selecting the appropriate polymers, the delivery profile of the respiratory dispersion may be tailored to optimize the effectiveness of the bioactive agent (column 18, lines 8-11). Antioxidants may also be incorporated into the dispersions, including sodium citrate and sodium ascorbate (column 18, lines 33-37). Morphine is discloses as a medicant or bioactive agent suitable for use in the dispersion (column 19, lines 45-47). The suspensions mediums additionally comprise fluorochemicals, with are also bacteriostatic thereby decreasing the potential for microbial growth in compatible preparations (column 5, line 66 through column 6. line 11). The examiner is interpreting the fluorochemicals to be antimicrobial agents.

Dellamary further discloses the precise amount of bioactive agent incorporated into the stabilized dispersions is dependent upon the agent of choice, the volume of suspension media required to effectively distribute the drug, the required dose and the form of the drug actually used for incorporation. Those skilled in the art will appreciate that; such determination may be made by using well-known pharmacological techniques in combination with the teachings of the Dellamary disclosure (column 19, lines 13-21).

Dellamary does not disclose the morphine is morphine base monohydrate.

The Merck index discloses generic morphine is in monohydrate form.

Applicants have defined the antioxidants as being used to adjust the pH of the composition (Specification, page 8, lines 3-11); therefore, it is the examiners position that it would have been obvious to a person of ordinary skill in the art to use

methanesulphonic acid, citric acid, sodium citrate, or sodium ascorbate to adjust the pH of the composition. It is generally considered to be prime facie obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose in order to form a composition that is to be used for an identical purpose. The motivation for combining them flows from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose. As shown by the recited teachings, instant claims are no more than the combination of conventional components of pH adjusting components and antimicrobial agents. It therefore follows that the instant claims define prime facie obvious subject matter. Cf. In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

The instant claims differ from the references only in the specific percentage selected for the compositions. However, It would have been deemed prima Facie obvious to one having ordinary skill in the art at the time of the invention to optimize the percentage of active ingredient and the controlled releasing polymer, to prepare a composition containing a therapeutically effective amount of an active agent because the determination of a specific percentage having the optimum therapeutic effect is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the active compounds. Therefore, the invention as Whole has been prima face obvious to one of ordinary skill in the art at the time the invention was made.

Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various

transmucosal compositions having various amounts of the active agent and chitosan polymers is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. See In re Russell, 439 F.2d 1228 169 USPQ 426(CCPA 1971).

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant stated an Exhibit was attached to the response; however, the examiner was unable to locate any exhibit submitted.

Conclusion

No claims are allowable. Due to the new grounds of rejection, this action is made Non-Final. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa S. Mercier whose telephone number is (571) 272-9039. The examiner can normally be reached on 7:30am-4pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615